

SEQUENCE LISTING

<110> Donna T. Ward
William Gaarde
Brett P. Monia
Jacqueline Wyatt

<120> ANTISENSE MODULATION OF MEKK4 EXPRESSION

<130> RTS-0169

<160> 89

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<213> Artificial Sequence

<223> Antisense Oligonucleotide

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<210> 2

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<210> 3

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<213> Homo sapiens

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<221> CDS

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tct ccc ccc agc aca cct cga cag atg aaa cgc atg tca acc aaa cat 96
Ser Pro Pro Ser Thr Pro Arg Gln Met Lys Arg Met Ser Thr Lys His
20 25 30

cag agg aat aat gtg ggg agg cca gcc agt cgg tct aat ttg aaa gaa 144
Gln Arg Asn Asn Val Gly Arg Pro Ala Ser Arg Ser Asn Leu Lys Glu
35 40 45

aaa atg aat gca cca aat cag cct cca cat aaa gac act gga aaa aca 192
Lys Met Asn Ala Pro Asn Gln Pro Pro His Lys Asp Thr Gly Lys Thr
50 55 60

gtg gag aat gtg gaa gaa tac agc tat aag cag gag aaa aag atc cga 240
Val Glu Asn Val Glu Glu Tyr Ser Tyr Lys Gln Glu Lys Lys Ile Arg
65 70 75 80

gca gct ctt aga aca aca gag cgt gat cat aaa aaa aat gta cag tgc 288
Ala Ala Leu Arg Thr Thr Glu Arg Asp His Lys Lys Asn Val Gln Cys
85 90 95

tca ttc atg tta gac tca gtg ggt gga tct ttg cca aaa aaa tca att 336
Ser Phe Met Leu Asp Ser Val Gly Gly Ser Leu Pro Lys Lys Ser Ile
100 105 110

cca gat gtg gat ctc aat aag cct tac ctc agc ctt ggc tgt agc aat 384
Pro Asp Val Asp Leu Asn Lys Pro Tyr Leu Ser Leu Gly Cys Ser Asn
115 120 125

gct aag ctt cca gta tct gtg ccc atg cct ata gcc aga cct gca cgc 432
Ala Lys Leu Pro Val Ser Val Pro Met Pro Ile Ala Arg Pro Ala Arg
130 135 140

cag act tct agg act gac tgt cca gca gat cgt tta aag ttt ttt gaa 480
Gln Thr Ser Arg Thr Asp Cys Pro Ala Asp Arg Leu Lys Phe Phe Glu
145 150 155 160

act tta cga ctt ttg cta aag ctt acc tca gtc tca aag aaa aaa gac 528
 Thr Leu Arg Leu Leu Leu Lys Leu Thr Ser Val Ser Lys Lys Lys Asp
 165 170 175

agg gag caa aga gga caa gaa aat acg tct ggt ttc tgg ctt aac cga 576
 Arg Glu Gln Arg Gly Gln Glu Asn Thr Ser Gly Phe Trp Leu Asn Arg
 180 185 190

tct aac gaa ctg atc tgg tta gag cta caa gcc tgg cat gca gga cgg 624
 Ser Asn Glu Leu Ile Trp Leu Glu Leu Gln Ala Trp His Ala Gly Arg
 195 200 205

aca att aac gac cag gac ttc ttt tta tat aca gcc cgt caa gcc atc 672
 Thr Ile Asn Asp Gln Asp Phe Phe Leu Tyr Thr Ala Arg Gln Ala Ile
 210 215 220

cca gat att att aat gaa atc ctt act ttc aaa gtc gac tat ggg agc 720
 Pro Asp Ile Ile Asn Glu Ile Leu Thr Phe Lys Val Asp Tyr Gly Ser
 225 230 235 240

ttc gcc ttt gtt aga gat aga gct ggt ttt aat ggt act tca gta gaa 768
 Phe Ala Phe Val Arg Asp Arg Ala Gly Phe Asn Gly Thr Ser Val Glu
 245 250 255

ggg cag tgc aaa gcc act cct gga aca aag att gta ggt tac tca aca 816
 Gly Gln Cys Lys Ala Thr Pro Gly Thr Lys Ile Val Gly Tyr Ser Thr
 260 265 270

cat cat gag cat ctc caa cgc cag agg gtc tca ttt gag cag gta aaa 864
 His His Glu His Leu Gln Arg Gln Arg Val Ser Phe Glu Gln Val Lys
 275 280 285

cgg ata atg gag ctg cta gag tac ata gaa gca ctt tat cca tca ttg 912
 Arg Ile Met Glu Leu Leu Glu Tyr Ile Glu Ala Leu Tyr Pro Ser Leu
 290 295 300

cag gct ctt cag aag gac tat gaa aaa tat gct gca aaa gac ttc cag 960
 Gln Ala Leu Gln Lys Asp Tyr Glu Lys Tyr Ala Ala Lys Asp Phe Gln
 305 310 315 320

gac agg gtg cag gca ctc tgt ttg tgg tta aac atc aca aaa gac tta 1008
 Asp Arg Val Gln Ala Leu Cys Leu Trp Leu Asn Ile Thr Lys Asp Leu
 325 330 335

aat cag aaa tta agg att atg ggc act gtt ttg ggc atc aag aat tta 1056
Asn Gln Lys Leu Arg Ile Met Gly Thr Val Leu Gly Ile Lys Asn Leu
340 345 350

tca gac att ggc tgg cca gtg ttt gaa atc cct tcc cct cga cca tcc 1104
Ser Asp Ile Gly Trp Pro Val Phe Glu Ile Pro Ser Pro Arg Pro Ser
355 360 365

aaa ggt aat gag ccg gag tat gag ggt gat gac aca gaa gga gaa tta 1152
Lys Gly Asn Glu Pro Glu Tyr Glu Gly Asp Asp Thr Glu Gly Glu Leu
370 375 380

aag gag ttg gaa agt agt acg gat gag agt gaa gaa gaa caa atc tct 1200
Lys Glu Leu Glu Ser Ser Thr Asp Glu Ser Glu Glu Glu Gln Ile Ser
385 390 395 400

gat cct agg gta ccg gaa atc aga cag ccc ata gat aac agc ttc gac 1248
Asp Pro Arg Val Pro Glu Ile Arg Gln Pro Ile Asp Asn Ser Phe Asp
405 410 415

atc cag tcg cgg gac tgc ata tcc aag aag ctt gag agg ctc gaa tct 1296
Ile Gln Ser Arg Asp Cys Ile Ser Lys Lys Leu Glu Arg Leu Glu Ser
420 425 430

gag gat gat tct ctt ggc tgg gga gca cca gac tgg agc aca gaa gca 1344
Glu Asp Asp Ser Leu Gly Trp Gly Ala Pro Asp Trp Ser Thr Glu Ala
435 440 445

ggc ttt agt aga cat tgt ctg act tct att tat aga cca ttt gta gac 1392
Gly Phe Ser Arg His Cys Leu Thr Ser Ile Tyr Arg Pro Phe Val Asp
450 455 460

aaa gca ctg aag cag atg ggg tta aga aag tta att tta aga ctt cac 1440
Lys Ala Leu Lys Gln Met Gly Leu Arg Lys Leu Ile Leu Arg Leu His
465 470 475 480

aag cta atg gat ggt tcc ttg caa agg gca cgt ata gca ttg gta aag 1488
Lys Leu Met Asp Gly Ser Leu Gln Arg Ala Arg Ile Ala Leu Val Lys
485 490 495

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Asn Asp Arg Pro Val Glu Phe Ser Glu Phe Pro Asp Pro Met Trp Gly
500 505 510

tca gat tat gtg cag ttg tca agg aca cca cct tca tct gag gag aaa 1584
Ser Asp Tyr Val Gln Leu Ser Arg Thr Pro Pro Ser Ser Glu Glu Lys
515 520 525

tgc agt gct gtg tcg tgg gag gag ctg aag gcc atg gat tta cct tca 1632
Cys Ser Ala Val Ser Trp Glu Glu Leu Lys Ala Met Asp Leu Pro Ser
530 535 540

ttc gaa cct gcc ttc cta gtt ctc tgc cga gtc ctt ctg aat gtc ata 1680
Phe Glu Pro Ala Phe Leu Val Leu Cys Arg Val Leu Leu Asn Val Ile
545 550 555 560

cat gag tgt ctg aag tta aga ttg gag cag aga cct gct gga gaa cca 1728
His Glu Cys Leu Lys Leu Arg Leu Glu Gln Arg Pro Ala Gly Glu Pro
565 570 575

tct ctc ttg agt att aag cag ctg gtg aga gag tgt aag gag gtc ctg 1776
Ser Leu Leu Ser Ile Lys Gln Leu Val Arg Glu Cys Lys Glu Val Leu
580 585 590

aag ggc ggc ctg ctg atg aag cag tac tac cag ttc atg ctg cag gag 1824
Lys Gly Gly Leu Leu Met Lys Gln Tyr Tyr Gln Phe Met Leu Gln Glu
595 600 605

gtt ctg gag gac ttg gag aag ccc gac tgc aac att gac gct ttt gaa 1872
Val Leu Glu Asp Leu Glu Lys Pro Asp Cys Asn Ile Asp Ala Phe Glu
610 615 620

gag gat cta cat aaa atg ctt atg gtg tat ttt gat tac atg aga agc 1920
Glu Asp Leu His Lys Met Leu Met Val Tyr Phe Asp Tyr Met Arg Ser
625 630 635 640

tgg atc caa atg cta cag caa tta cct caa gca tcg cat agt tta aaa 1968
Trp Ile Gln Met Leu Gln Gln Leu Pro Gln Ala Ser His Ser Leu Lys
645 650 655

aat ctg tta gaa gaa gaa tgg aat ttc acc aaa gaa ata act cat tac 2016
Asn Leu Leu Glu Glu Trp Asn Phe Thr Lys Glu Ile Thr His Tyr
660 665 670

ata cgg gga gga gaa gca cag gcc ggg aag ctt ttc tgt gac att gca 2064
Ile Arg Gly Gly Glu Ala Gln Ala Gly Lys Leu Phe Cys Asp Ile Ala
675 680 685

gga atg ctg ctg aaa tct aca gga agt ttt tta gaa ttt ggc tta cag 2112
Gly Met Leu Leu Lys Ser Thr Gly Ser Phe Leu Glu Phe Gly Leu Gln
690 695 700

gag agc tgt gct gaa ttt tgg act agt gcg gat gac agc agt gct tcc 2160
Glu Ser Cys Ala Glu Phe Trp Thr Ser Ala Asp Asp Ser Ser Ala Ser
705 710 715 720

gac gaa atc agg agg tct gtt ata gag atc agt cga gcc ctg aag gag 2208
Asp Glu Ile Arg Arg Ser Val Ile Glu Ile Ser Arg Ala Leu Lys Glu
725 730 735

ctc ttc cat gaa gcc aga gaa agg gct tcc aaa gca ctt gga ttt gct 2256
Leu Phe His Glu Ala Arg Glu Arg Ala Ser Lys Ala Leu Gly Phe Ala
740 745 750

aaa atg ttg aga aag gac ctg gaa ata gca gca gaa ttc agg ctt tca 2304
Lys Met Leu Arg Lys Asp Leu Glu Ile Ala Ala Glu Phe Arg Leu Ser
755 760 765

gcc cca gtt aga gac ctc ctg gat gtt ctg aaa tca aaa cag tat gtc 2352
Ala Pro Val Arg Asp Leu Leu Asp Val Leu Lys Ser Lys Gln Tyr Val
770 775 780

aag gtg caa att cct ggg tta gaa aac ttg caa atg ttt gtt cca gac 2400
Lys Val Gln Ile Pro Gly Leu Glu Asn Leu Gln Met Phe Val Pro Asp
785 790 795 800

act ctt gct gag gag aag agt att att ttg cag tta ctc aat gca gct 2448
Thr Leu Ala Glu Glu Lys Ser Ile Ile Leu Gln Leu Leu Asn Ala Ala
805 810 815

gca gga aag gac tgt tca aaa gat tca gat gac gta ctc atc gat gcc 2496
Ala Gly Lys Asp Cys Ser Lys Asp Ser Asp Asp Val Leu Ile Asp Ala
820 825 830

tat ctg ctt ctg acc aag cac ggt gat cga gcc cgt gat tca gag gac 2544
Tyr Leu Leu Leu Thr Lys His Gly Asp Arg Ala Arg Asp Ser Glu Asp
835 840 845

agc tgg ggc acc tgg gag gca cag cct gtc aaa gtc gtg cct cag gtg 2592
Ser Trp Gly Thr Trp Glu Ala Gln Pro Val Lys Val Val Pro Gln Val
850 855 860

gag act gtt gac acc ctg aga agc atg cag gtg gat aat ctt tta cta 2640
Glu Thr Val Asp Thr Leu Arg Ser Met Gln Val Asp Asn Leu Leu Leu
865 870 875 880

gtt gtc atg cag tct gcg cat ctc aca att cag aga aaa gct ttc cag 2688
Val Val Met Gln Ser Ala His Leu Thr Ile Gln Arg Lys Ala Phe Gln
885 890 895

cag tcc att gag gga ctt atg act ctg tgc cag gag cag aca tcc agt 2736
Gln Ser Ile Glu Gly Leu Met Thr Leu Cys Gln Glu Gln Thr Ser Ser
900 905 910

cag ccg gtc atc gcc aaa gct ttg cag cag ctg aag aat gat gca ttg 2784
Gln Pro Val Ile Ala Lys Ala Leu Gln Gln Leu Lys Asn Asp Ala Leu
915 920 925

gag cta tgc aac agg ata agc aat gcc att gac cgc gtg gac cac atg 2832
Glu Leu Cys Asn Arg Ile Ser Asn Ala Ile Asp Arg Val Asp His Met
930 935 940

ttc aca tca gaa ttt gat gct gag gtt gat gaa tct gaa tct gtc acc 2880
Phe Thr Ser Glu Phe Asp Ala Glu Val Asp Glu Ser Glu Ser Val Thr
945 950 955 960

ttg caa cag tac tac cga gaa gca atg att cag ggg tac aat ttt gga 2928
Leu Gln Gln Tyr Tyr Arg Glu Ala Met Ile Gln Gly Tyr Asn Phe Gly
965 970 975

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Phe Glu Tyr His Lys Glu Val Val Arg Leu Met Ser Gly Glu Phe Arg
980 985 990

cag aag ata gga gac aaa tat ata agc ttt gcc cgg aag tgg atg aat 3024
Gln Lys Ile Gly Asp Lys Tyr Ile Ser Phe Ala Arg Lys Trp Met Asn
995 1000 1005

tat gtc ctg act aaa tgt gag agt ggt aga ggt aca aga ccc agg tgg 3072
Tyr Val Leu Thr Lys Cys Glu Ser Gly Arg Gly Thr Arg Pro Arg Trp
1010 1015 1020

gcg act caa gga ttt gat ttt cta caa gca att gaa cct gcc ttt att 3120
Ala Thr Gln Gly Phe Asp Phe Leu Gln Ala Ile Glu Pro Ala Phe Ile
1025 1030 1035 1040

tca gct tta cca gaa gat gac ttc ttg agt tta caa gcc ttg atg aat 3168
Ser Ala Leu Pro Glu Asp Asp Phe Leu Ser Leu Gln Ala Leu Met Asn
1045 1050 1055

gaa tgc att ggc cat gtc ata gga aaa cca cac agt cct gtt aca ggt 3216
Glu Cys Ile Gly His Val Ile Gly Lys Pro His Ser Pro Val Thr Gly
1060 1065 1070

ttg tac ctt gcc att cat cgg aac agc ccc cgt cct atg aag gta cct 3264
Leu Tyr Leu Ala Ile His Arg Asn Ser Pro Arg Pro Met Lys Val Pro
1075 1080 1085

cga tgc cat agt gac cct cct aac cca cac ctc att atc ccc act cca 3312
Arg Cys His Ser Asp Pro Pro Asn Pro His Leu Ile Ile Pro Thr Pro
1090 1095 1100

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1105 1110 1115 1120

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1125 1130 1135

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Thr Glu Glu Arg Asp Glu Pro Ala Tyr Pro Arg Gly Asp Ser Ser Gly
1140 1145 1150

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Ser Thr Arg Arg Ser Trp Glu Leu Arg Thr Leu Ile Ser Gln Ser Lys
1155 1160 1165

gat act gct tct aaa cta gga ccc ata gaa gct atc cag aag tca gtc 3552
Asp Thr Ala Ser Lys Leu Gly Pro Ile Glu Ala Ile Gln Lys Ser Val
1170 1175 1180

cga ttg ttt gaa gaa aag agg tac cga gaa atg agg aga aag aat atc 3600
Arg Leu Phe Glu Glu Lys Arg Tyr Arg Glu Met Arg Arg Lys Asn Ile
1185 1190 1195 1200

att ggt caa gtt tgt gat acg cct aag tcc tat gat aat gtt atg cac 3648
Ile Gly Gln Val Cys Asp Thr Pro Lys Ser Tyr Asp Asn Val Met His
1205 1210 1215

gtt ggc ttg agg aag gtg acc ttc aaa tgg caa aga gga aac aaa att 3696
Val Gly Leu Arg Lys Val Thr Phe Lys Trp Gln Arg Gly Asn Lys Ile
1220 1225 1230

gga gaa ggc cag tat ggg aag gtg tac acc tgc atc agc gtc gac acc 3744
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1235 1240 1245

ggg gag ctg atg gcc atg aaa gag att cga ttt caa cct aat gac cat 3792
Gly Glu Leu Met Ala Met Lys Glu Ile Arg Phe Gln Pro Asn Asp His
1250 1255 1260

aag act atc aag gaa act gca gac gaa ttg aaa ata ttc gaa ggc atc 3840
Lys Thr Ile Lys Glu Thr Ala Asp Glu Leu Lys Ile Phe Glu Gly Ile
1265 1270 1275 1280

aaa cac ccc aat ctg gtt cgg tat ttt ggt gtg gag ctc cat aga gaa 3888
Lys His Pro Asn Leu Val Arg Tyr Phe Gly Val Glu Leu His Arg Glu
1285 1290 1295

gaa atg tac atc ttc atg gag tac tgc gat gag ggg act tta gaa gag 3936
Glu Met Tyr Ile Phe Met Glu Tyr Cys Asp Glu Gly Thr Leu Glu Glu
1300 1305 1310

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Val Ser Arg Leu Gly Leu Gln Glu His Val Ile Arg Leu Tyr Ser Lys
1315 1320 1325

cag atc acc att gcg atc aac gtc ctc cat gag cat ggc ata gtc cac 4032
Gln Ile Thr Ile Ala Ile Asn Val Leu His Glu His Gly Ile Val His
1330 1335 1340

cgt gac att aaa ggt gcc aat atc ttc ctt acc tca tct gga tta atc 4080
Arg Asp Ile Lys Gly Ala Asn Ile Phe Leu Thr Ser Ser Gly Leu Ile
1345 1350 1355 1360

aaa ctg gga gat ttt gga tgt tca gta aag ctc aaa aac aat gcc cag 4128
Lys Leu Gly Asp Phe Gly Cys Ser Val Lys Leu Lys Asn Asn Ala Gln
1365 1370 1375

acc atg cct ggt gaa gtg aac agc acc ctg ggg aca gca gca tac atg 4176
Thr Met Pro Gly Glu Val Asn Ser Thr Leu Gly Thr Ala Ala Tyr Met
1380 1385 1390

gca cct gaa gtc atc act cgt gcc aaa gga gag ggc cat ggg cgt gcg 4224
Ala Pro Glu Val Ile Thr Arg Ala Lys Gly Glu Gly His Gly Arg Ala
1395 1400 1405

gcc gac atc tgg agt ctg ggg tgt gtt gtc ata gag atg gtg act ggc 4272
Ala Asp Ile Trp Ser Leu Gly Cys Val Val Ile Glu Met Val Thr Gly
1410 1415 1420

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Lys Arg Pro Trp His Glu Tyr Glu His Asn Phe Gln Ile Met Tyr Lys
1425 1430 1435 1440

gtg ggg atg gga cat aag cca cca atc cct gaa aga tta agc cct gaa 4368
Val Gly Met Gly His Lys Pro Pro Ile Pro Glu Arg Leu Ser Pro Glu
1445 1450 1455

gga aag gac ttc ctt tct cac tgc ctt gag agt gac cca aag atg aga 4416
Gly Lys Asp Phe Leu Ser His Cys Leu Glu Ser Asp Pro Lys Met Arg
1460 1465 1470

tgg acc gcc agc cag ctc ctc gac cat tcg ttt gtc aag gtt tgc aca 4464
Trp Thr Ala Ser Gln Leu Leu Asp His Ser Phe Val Lys Val Cys Thr
1475 1480 1485

gat gaa gaa tga agcctagtag aatatggact tggaaaattc tcttaatcac 4516
Asp Glu Glu XXX
1490

tactgtatgt aatatattaca taaagactgt gctgagaagc agtataagcc tttttaacct 4576

tccaagactg aagactgcac aggtgacaag cgtcacttct cctgctgctc ctgtttgtct 4636

gatgtggcaa aaggccctct ggagggctgg tggccacgag gttaaagaag ctgcatgtta 4696

agtgccatta ctactgtaca cggaccatcg cctctgtctc ctccgtgtct cgcgcgactg 4756

agaaccgtga catcagcgta gtgttttgac ctttctaggt tcaaaagaag ttgtagtgtt 4816

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ctttaccttt tttgttggtg ttggcaagct gcaggtttgt aatgcaaaag gctgattact 4936

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28

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<400> 5

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<210> 6

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<213> Artificial Sequence

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26

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<223> PCR Primer

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21

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<213> Artificial Sequence

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21

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<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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ccatgcgggg ctccgtgcac gg atg aga gaa gcc gct gcc gcg ctg gtc cct 172

Met Arg Glu Ala Ala Ala Ala Leu Val Pro

1

5

10

cct ccc gcc ttt gcc gtc acg cct gcc gcc gcc atg gag gag ccg ccg 220

Pro Pro Ala Phe Ala Val Thr Pro Ala Ala Ala Met Glu Glu Pro Pro

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cca ccg ccg ccg ccg cca cca ccg cca ccg gaa ccc gag acc gag tca				268
Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro Glu Pro Glu Thr Glu Ser				
	30	35	40	
gaa ccc gag tgc tgc ttg gcg gcg agg caa gag ggc aca ttg gga gat				316
Glu Pro Glu Cys Cys Leu Ala Ala Arg Gln Glu Gly Thr Leu Gly Asp				
	45	50	55	
tca gct tgc aag agt cct gaa tct gat cta gaa gac ttc tcc gat gaa				364
Ser Ala Cys Lys Ser Pro Glu Ser Asp Leu Glu Asp Phe Ser Asp Glu				
	60	65	70	
aca aat aca gag aat ctt tat ggt acc tct ccc ccc agc aca cct cga				412
Thr Asn Thr Glu Asn Leu Tyr Gly Thr Ser Pro Pro Ser Thr Pro Arg				
	75	80	85	90
cag atg aaa cgc atg tca acc aaa cat cag agg aat aat gtg ggg agg				460
Gln Met Lys Arg Met Ser Thr Lys His Gln Arg Asn Asn Val Gly Arg				
	95	100	105	
cca gcc agt cgg tct aat ttg aaa gaa aaa atg aat gca cca aat cag				508
Pro Ala Ser Arg Ser Asn Leu Lys Glu Lys Met Asn Ala Pro Asn Gln				
	110	115	120	
cct cca cat aaa gac act gga aaa aca gtg gag aat gtg gaa gaa tac				556
Pro Pro His Lys Asp Thr Gly Lys Thr Val Glu Asn Val Glu Glu Tyr				
	125	130	135	
agc tat aag cag gag aaa aag atc cga gca gct ctt aga aca aca gag				604
Ser Tyr Lys Gln Glu Lys Lys Ile Arg Ala Ala Leu Arg Thr Thr Glu				
	140	145	150	
cgt gat cat aaa aaa aat gta cag tgc tca ttc atg tta gac tca gtg				652
Arg Asp His Lys Lys Asn Val Gln Cys Ser Phe Met Leu Asp Ser Val				
	155	160	165	170
ggg gga tct ttg cca aaa aaa tca att cca gat gtg gat ctc aat aag				700
Gly Gly Ser Leu Pro Lys Lys Ser Ile Pro Asp Val Asp Leu Asn Lys				
	175	180	185	
cct tac ctc agc ctt ggc tgt agc aat gct aag ctt cca gta tct gtg				748
Pro Tyr Leu Ser Leu Gly Cys Ser Asn Ala Lys Leu Pro Val Ser Val				

190	195	200	
ccc atg cct ata gcc aga cct gca cgc cag act tct agg act gac tgt			796
Pro Met Pro Ile Ala Arg Pro Ala Arg Gln Thr Ser Arg Thr Asp Cys			
205	210	215	
cca gca gat cgt tta aag ttt ttt gaa act tta cga ctt ttg cta aag			844
Pro Ala Asp Arg Leu Lys Phe Phe Glu Thr Leu Arg Leu Leu Leu Lys			
220	225	230	
ctt acc tca gtc tca aag aaa aaa gac agg gag caa aga gga caa gaa			892
Leu Thr Ser Val Ser Lys Lys Lys Asp Arg Glu Gln Arg Gly Gln Glu			
235	240	245	250
aat acg tct ggt ttc tgg ctt aac cga tct aac gaa ctg atc tgg tta			940
Asn Thr Ser Gly Phe Trp Leu Asn Arg Ser Asn Glu Leu Ile Trp Leu			
255	260	265	
gag cta caa gcc tgg cat gca gga cgg aca att aac gac cag gac ttc			988
Glu Leu Gln Ala Trp His Ala Gly Arg Thr Ile Asn Asp Gln Asp Phe			
270	275	280	
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Phe Leu Tyr Thr Ala Arg Gln Ala Ile Pro Asp Ile Ile Asn Glu Ile			
285	290	295	
ctt act ttc aaa gtc gac tat ggg agc ttc gcc ttt gtt aga gat aga			1084
Leu Thr Phe Lys Val Asp Tyr Gly Ser Phe Ala Phe Val Arg Asp Arg			
300	305	310	
gct ggt ttt aat ggt act tca gta gaa ggg cag tgc aaa gcc act cct			1132
Ala Gly Phe Asn Gly Thr Ser Val Glu Gly Gln Cys Lys Ala Thr Pro			
315	320	325	330
gga aca aag att gta ggt tac tca aca cat cat gag cat ctc caa cgc			1180
Gly Thr Lys Ile Val Gly Tyr Ser Thr His His Glu His Leu Gln Arg			
335	340	345	
cag agg gtc tca ttt gag cag gta aaa cgg ata atg gag ctg cta gag			1228
Gln Arg Val Ser Phe Glu Gln Val Lys Arg Ile Met Glu Leu Leu Glu			
350	355	360	
tac ata gaa gca ctt tat cca tca ttg cag gct ctt cag aag gac tat			1276
Tyr Ile Glu Ala Leu Tyr Pro Ser Leu Gln Ala Leu Gln Lys Asp Tyr			

365	370	375	
gaa aaa tat gct gca aaa gac ttc cag gac agg gtg cag gca ctc tgt			1324
Glu Lys Tyr Ala Ala Lys Asp Phe Gln Asp Arg Val Gln Ala Leu Cys			
380	385	390	
ttg tgg tta aac atc aca aaa gac tta aat cag aaa tta agg att atg			1372
Leu Trp Leu Asn Ile Thr Lys Asp Leu Asn Gln Lys Leu Arg Ile Met			
395	400	405	410
ggc act gtt ttg ggc atc aag aat tta tca gac att ggc tgg cca gtg			1420
Gly Thr Val Leu Gly Ile Lys Asn Leu Ser Asp Ile Gly Trp Pro Val			
415	420	425	
ttt gaa atc cct tcc cct cga cca tcc aaa ggt aat gag ccg gag tat			1468
Phe Glu Ile Pro Ser Pro Arg Pro Ser Lys Gly Asn Glu Pro Glu Tyr			
430	435	440	
gag ggt gat gac aca gaa gga gaa tta aag gag ttg gaa agt agt acg			1516
Glu Gly Asp Asp Thr Glu Gly Glu Leu Lys Glu Leu Glu Ser Ser Thr			
445	450	455	
gat gag agt gaa gaa gaa caa atc tct gat cct agg gta ccg gaa atc			1564
Asp Glu Ser Glu Glu Glu Gln Ile Ser Asp Pro Arg Val Pro Glu Ile			
460	465	470	
aga cag ccc ata gat aac agc ttc gac atc cag tcg cgg gac tgc ata			1612
Arg Gln Pro Ile Asp Asn Ser Phe Asp Ile Gln Ser Arg Asp Cys Ile			
475	480	485	490
tcc aag aag ctt gag agg ctc gaa tct gag gat gat tct ctt ggc tgg			1660
Ser Lys Lys Leu Glu Arg Leu Glu Ser Glu Asp Asp Ser Leu Gly Trp			
495	500	505	
gga gca cca gac tgg agc aca gaa gca ggc ttt agt aga cat tgt ctg			1708
Gly Ala Pro Asp Trp Ser Thr Glu Ala Gly Phe Ser Arg His Cys Leu			
510	515	520	
act tct att tat aga cca ttt gta gac aaa gca ctg aag cag atg ggg			1756
Thr Ser Ile Tyr Arg Pro Phe Val Asp Lys Ala Leu Lys Gln Met Gly			
525	530	535	
tta aga aag tta att tta aga ctt cac aag cta atg gat ggt tcc ttg			1804
Leu Arg Lys Leu Ile Leu Arg Leu His Lys Leu Met Asp Gly Ser Leu			

540	545	550	
caa agg gca cgt ata gca ttg gta aag aac gat cgt cca gtg gag ttt			1852
Gln Arg Ala Arg Ile Ala Leu Val Lys Asn Asp Arg Pro Val Glu Phe			
555	560	565	570
tct gaa ttt cca gat ccc atg tgg ggt tca gat tat gtg cag ttg tca			1900
Ser Glu Phe Pro Asp Pro Met Trp Gly Ser Asp Tyr Val Gln Leu Ser			
	575	580	585
agg aca cca cct tca tct gag gag aaa tgc agt gct gtg tcg tgg gag			1948
Arg Thr Pro Pro Ser Ser Glu Glu Lys Cys Ser Ala Val Ser Trp Glu			
	590	595	600
gag ctg aag gcc atg gat tta cct tca ttc gaa cct gcc ttc cta gtt			1996
Glu Leu Lys Ala Met Asp Leu Pro Ser Phe Glu Pro Ala Phe Leu Val			
	605	610	615
ctc tgc cga gtc ctt ctg aat gtc ata cat gag tgt ctg aag tta aga			2044
Leu Cys Arg Val Leu Leu Asn Val Ile His Glu Cys Leu Lys Leu Arg			
	620	625	630
ttg gag cag aga cct gct gga gaa cca tct ctc ttg agt att aag cag			2092
Leu Glu Gln Arg Pro Ala Gly Glu Pro Ser Leu Leu Ser Ile Lys Gln			
	635	640	645
ctg gtg aga gag tgt aag gag gtc ctg aag ggc ggc ctg ctg atg aag			2140
Leu Val Arg Glu Cys Lys Glu Val Leu Lys Gly Gly Leu Leu Met Lys			
	655	660	665
cag tac tac cag ttc atg ctg cag gag gtt ctg gag gac ttg gag aag			2188
Gln Tyr Tyr Gln Phe Met Leu Gln Glu Val Leu Glu Asp Leu Glu Lys			
	670	675	680
ccc gac tgc aac att gac gct ttt gaa gag gat cta cat aaa atg ctt			2236
Pro Asp Cys Asn Ile Asp Ala Phe Glu Glu Asp Leu His Lys Met Leu			
	685	690	695
atg gtg tat ttt gat tac atg aga agc tgg atc caa atg cta cag caa			2284
Met Val Tyr Phe Asp Tyr Met Arg Ser Trp Ile Gln Met Leu Gln Gln			
	700	705	710
tta cct caa gca tcg cat agt tta aaa aat ctg tta gaa gaa gaa tgg			2332
Leu Pro Gln Ala Ser His Ser Leu Lys Asn Leu Leu Glu Glu Glu Trp			

715	720	725	730	
aat ttc acc aaa gaa ata act cat tac ata cgg gga gga gaa gca cag				2380
Asn Phe Thr Lys Glu Ile Thr His Tyr Ile Arg Gly Gly Glu Ala Gln				
	735	740	745	
gcc ggg aag ctt ttc tgt gac att gca gga atg ctg ctg aaa tct aca				2428
Ala Gly Lys Leu Phe Cys Asp Ile Ala Gly Met Leu Leu Lys Ser Thr				
	750	755	760	
gga agt ttt tta gaa ttt ggc tta cag gag agc tgt gct gaa ttt tgg				2476
Gly Ser Phe Leu Glu Phe Gly Leu Gln Glu Ser Cys Ala Glu Phe Trp				
	765	770	775	
act agt gcg gat gac agc agt gct tcc gac gaa atc atc agg tct gtt				2524
Thr Ser Ala Asp Asp Ser Ser Ala Ser Asp Glu Ile Ile Arg Ser Val				
	780	785	790	
ata gag atc agt cga gcc ctg aag gag ctc ttc cat gaa gcc aga gaa				2572
Ile Glu Ile Ser Arg Ala Leu Lys Glu Leu Phe His Glu Ala Arg Glu				
	795	800	805	810
agg gct tcc aaa gca ctt gga ttt gct aaa atg ttg aga aag gac ctg				2620
Arg Ala Ser Lys Ala Leu Gly Phe Ala Lys Met Leu Arg Lys Asp Leu				
	815	820	825	
gaa ata gca gca gaa ttc agg ctt tca gcc cca gtt aga gac ctc ctg				2668
Glu Ile Ala Ala Glu Phe Arg Leu Ser Ala Pro Val Arg Asp Leu Leu				
	830	835	840	
gat gtt ctg aaa tca aaa cag tat gtc aag gtg caa att cct ggg tta				2716
Asp Val Leu Lys Ser Lys Gln Tyr Val Lys Val Gln Ile Pro Gly Leu				
	845	850	855	
gaa aac ttg caa atg ttt gtt cca gac act ctt gct gag gag aag agt				2764
Glu Asn Leu Gln Met Phe Val Pro Asp Thr Leu Ala Glu Glu Lys Ser				
	860	865	870	
att att ttg cag tta ctc aat gca gct gca gga aag gac tgt tca aaa				2812
Ile Ile Leu Gln Leu Leu Asn Ala Ala Ala Gly Lys Asp Cys Ser Lys				
	875	880	885	890
gat tca gat gac gta ctc atc gat gcc tat ctg ctt ctg acc aag cac				2860
Asp Ser Asp Asp Val Leu Ile Asp Ala Tyr Leu Leu Leu Thr Lys His				

895	900	905	
ggt gat cga gcc cgt gat tca gag gac agc tgg ggc acc tgg gag gca			2908
Gly Asp Arg Ala Arg Asp Ser Glu Asp Ser Trp Gly Thr Trp Glu Ala			
910	915	920	
cag cct gtc aaa gtc gtg cct cag gtg gag act gtt gac acc ctg aga			2956
Gln Pro Val Lys Val Val Pro Gln Val Glu Thr Val Asp Thr Leu Arg			
925	930	935	
agc atg cag gtg gat aat ctt tta cta gtt gtc atg cag tct gcg cat			3004
Ser Met Gln Val Asp Asn Leu Leu Leu Val Val Met Gln Ser Ala His			
940	945	950	
ctc aca att cag aga aaa gct ttc cag cag tcc att gag gga ctt atg			3052
Leu Thr Ile Gln Arg Lys Ala Phe Gln Gln Ser Ile Glu Gly Leu Met			
955	960	965	970
act ctg tgc cag gag cag aca tcc agt cag ccg gtc atc gcc aaa gct			3100
Thr Leu Cys Gln Glu Gln Thr Ser Ser Gln Pro Val Ile Ala Lys Ala			
975	980	985	
ttg cag cag ctg aag aat gat gca ttg gag cta tgc aac agg ata agc			3148
Leu Gln Gln Leu Lys Asn Asp Ala Leu Glu Leu Cys Asn Arg Ile Ser			
990	995	1000	
aat gcc att gac cgc gtg gac cac atg ttc aca tca gaa ttt gat gct			3196
Asn Ala Ile Asp Arg Val Asp His Met Phe Thr Ser Glu Phe Asp Ala			
1005	1010	1015	
gag gtt gat gaa tct gaa tct gtc acc ttg caa cag tac tac cga gaa			3244
Glu Val Asp Glu Ser Glu Ser Val Thr Leu Gln Gln Tyr Tyr Arg Glu			
1020	1025	1030	
gca atg att cag ggg tac aat ttt gga ttt gag tat cat aaa gaa gtt			3292
Ala Met Ile Gln Gly Tyr Asn Phe Gly Phe Glu Tyr His Lys Glu Val			
1035	1040	1045	1050
gtt cgt ttg atg tct ggg gag ttt aga cag aag ata gga gac aaa tat			3340
Val Arg Leu Met Ser Gly Glu Phe Arg Gln Lys Ile Gly Asp Lys Tyr			
1055	1060	1065	
ata agc ttt gcc cgg aag tgg atg aat tat gtc ctg act aaa tgt gag			3388
Ile Ser Phe Ala Arg Lys Trp Met Asn Tyr Val Leu Thr Lys Cys Glu			

1070	1075	1080	
agt ggt aga ggt aca aga ccc agg tgg gcg act caa gga ttt gat ttt			3436
Ser Gly Arg Gly Thr Arg Pro Arg Trp Ala Thr Gln Gly Phe Asp Phe			
1085	1090	1095	
cta caa gca att gaa cct gcc ttt att tca gct tta cca gaa gat gac			3484
Leu Gln Ala Ile Glu Pro Ala Phe Ile Ser Ala Leu Pro Glu Asp Asp			
1100	1105	1110	
ttc ttg agt tta caa gcc ttg atg aat gaa tgc att ggc cat gtc ata			3532
Phe Leu Ser Leu Gln Ala Leu Met Asn Glu Cys Ile Gly His Val Ile			
1115	1120	1125	1130
gga aaa cca cac agt cct gtt aca ggt ttg tac ctt gcc att cat cgg			3580
Gly Lys Pro His Ser Pro Val Thr Gly Leu Tyr Leu Ala Ile His Arg			
1135	1140	1145	
aac agc ccc cgt cct atg aag gta cct cga tgc cat agt gac cct cct			3628
Asn Ser Pro Arg Pro Met Lys Val Pro Arg Cys His Ser Asp Pro Pro			
1150	1155	1160	
aac cca cac ctc att atc ccc act cca gag gga ttc agc act cgg agc			3676
Asn Pro His Leu Ile Ile Pro Thr Pro Glu Gly Phe Ser Thr Arg Ser			
1165	1170	1175	
atg cct tcc gac gcg cgg agc cat ggc agc cct gct gct gct gct gct			3724
Met Pro Ser Asp Ala Arg Ser His Gly Ser Pro Ala Ala Ala Ala			
1180	1185	1190	
gct gct gct gct gtt gct gcc agt cgg ccc agc ccc tct ggt ggt gac			3772
Ala Ala Ala Ala Val Ala Ala Ser Arg Pro Ser Pro Ser Gly Gly Asp			
1195	1200	1205	1210
tct gtg ctg ccc aaa tcc atc agc agt gcc cat gat acc agg ggt tcc			3820
Ser Val Leu Pro Lys Ser Ile Ser Ser Ala His Asp Thr Arg Gly Ser			
1215	1220	1225	
agc gtt cct gaa aat gat cga ttg gct tcc ata gct gct gaa ttg cag			3868
Ser Val Pro Glu Asn Asp Arg Leu Ala Ser Ile Ala Ala Glu Leu Gln			
1230	1235	1240	
ttt agg tcc ctg agt cgt cac tca agc ccc acg gag gag cga gat gaa			3916
Phe Arg Ser Leu Ser Arg His Ser Ser Pro Thr Glu Glu Arg Asp Glu			

1245	1250	1255	
cca gca tat cca aga gga gat tca agt ggg tcc aca aga aga agt tgg			3964
Pro Ala Tyr Pro Arg Gly Asp Ser Ser Gly Ser Thr Arg Arg Ser Trp			
1260	1265	1270	
gaa ctt cgg aca cta atc agc cag agt aaa gat act gct tct aaa cta			4012
Glu Leu Arg Thr Leu Ile Ser Gln Ser Lys Asp Thr Ala Ser Lys Leu			
1275	1280	1285	1290
gga ccc ata gaa gct atc cag aag tca gtc cga ttg ttt gaa gaa aag			4060
Gly Pro Ile Glu Ala Ile Gln Lys Ser Val Arg Leu Phe Glu Glu Lys			
1295	1300	1305	
agg tac cga gaa atg agg aga aag aat atc att ggt caa gtt tgt gat			4108
Arg Tyr Arg Glu Met Arg Arg Lys Asn Ile Ile Gly Gln Val Cys Asp			
1310	1315	1320	
acg cct aag tcc tat gat aat gtt atg cac gtt ggc ttg agg aag gtg			4156
Thr Pro Lys Ser Tyr Asp Asn Val Met His Val Gly Leu Arg Lys Val			
1325	1330	1335	
acc ttc aaa tgg caa aga gga aac aaa att gga gaa ggc cag tat ggg			4204
Thr Phe Lys Trp Gln Arg Gly Asn Lys Ile Gly Glu Gly Gln Tyr Gly			
1340	1345	1350	
aag gtg tac acc tgc atc agc gtc gac acc ggg gag ctg atg gcc atg			4252
Lys Val Tyr Thr Cys Ile Ser Val Asp Thr Gly Glu Leu Met Ala Met			
1355	1360	1365	1370
aaa gag att cga ttt caa cct aat gac cat aag act atc aag gaa act			4300
Lys Glu Ile Arg Phe Gln Pro Asn Asp His Lys Thr Ile Lys Glu Thr			
1375	1380	1385	
gca gac gaa ttg aaa ata ttc gaa ggc atc aaa cac ccc aat ctg gtt			4348
Ala Asp Glu Leu Lys Ile Phe Glu Gly Ile Lys His Pro Asn Leu Val			
1390	1395	1400	
cgg tat ttt ggt gtg gag ctc cat aga gaa gaa atg tac atc ttc atg			4396
Arg Tyr Phe Gly Val Glu Leu His Arg Glu Glu Met Tyr Ile Phe Met			
1405	1410	1415	
gag tac tgc gat gag ggg act tta gaa gag gtg tca agg ctg gga ctt			4444
Glu Tyr Cys Asp Glu Gly Thr Leu Glu Glu Val Ser Arg Leu Gly Leu			

1420	1425	1430	
cag gaa cat gtg att agg ctg tat tca aag cag atc acc att gcg atc			4492
Gln Glu His Val Ile Arg Leu Tyr Ser Lys Gln Ile Thr Ile Ala Ile			
1435	1440	1445	1450
aac gtc ctc cat gag cat ggc ata gtc cac cgt gac att aaa ggt gcc			4540
Asn Val Leu His Glu His Gly Ile Val His Arg Asp Ile Lys Gly Ala			
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aat atc ttc ctt acc tca tct gga tta atc aaa ctg gga gat ttt gga			4588
Asn Ile Phe Leu Thr Ser Ser Gly Leu Ile Lys Leu Gly Asp Phe Gly			
1470	1475	1480	
tgt tca gta aag ctc aaa aac aat gcc cag acc atg cct ggt gaa gtg			4636
Cys Ser Val Lys Leu Lys Asn Asn Ala Gln Thr Met Pro Gly Glu Val			
1485	1490	1495	
aac agc acc ctg ggg aca gca gca tac atg gca cct gaa gtc atc act			4684
Asn Ser Thr Leu Gly Thr Ala Ala Tyr Met Ala Pro Glu Val Ile Thr			
1500	1505	1510	
cgt gcc aaa gga gag ggc cat ggg cgt gcg gcc gac atc tgg agt ctg			4732
Arg Ala Lys Gly Glu Gly His Gly Arg Ala Ala Asp Ile Trp Ser Leu			
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ggg tgt gtt gtc ata gag atg gtg act ggc aag agg cct tgg cat gag			4780
Gly Cys Val Val Ile Glu Met Val Thr Gly Lys Arg Pro Trp His Glu			
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tat gag cac aac ttt caa att atg tat aaa gtg ggg atg gga cat aag			4828
Tyr Glu His Asn Phe Gln Ile Met Tyr Lys Val Gly Met Gly His Lys			
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cca cca atc cct gaa aga tta agc cct gaa gga aag gac ttc ctt tct			4876
Pro Pro Ile Pro Glu Arg Leu Ser Pro Glu Gly Lys Asp Phe Leu Ser			
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cac tgc ctt gag agt gac cca aag atg aga tgg acc gcc agc cag ctc			4924
His Cys Leu Glu Ser Asp Pro Lys Met Arg Trp Thr Ala Ser Gln Leu			
1580	1585	1590	
ctc gac cat tcg ttt gtc aag gtt tgc aca gat gaa gaa tga agcctagtag			4976
Leu Asp His Ser Phe Val Lys Val Cys Thr Asp Glu Glu			

1595

1600

1605

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PATENT

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